REMARKS

Reconsideration and withdrawal of the rejections of the application are requested in view of the amendments and remarks presented herein, which place the application into condition for allowance.

The Examiner is thanked for indicating that the rejection under 35 U.S.C. § 112, in part, and the rejections under 35 U.S.C. § 102 have been withdrawn.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 2, 68-70, and 72-82 are pending in this application. Claims 1, 2, and 72 are amended, and claim 71 is cancelled without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

The amendment to claim 1 is to clarify R_5 and R_{10}, while the amendment to claims 2 and 72 are to perfect antecedent basis. No new matter is added.

It is submitted that the claims are patentably distinct over the prior art and that these claim are and were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE REJECTION UNDER 35 U.S.C. § 112 IS OVERCOME

Claims 1, 2, and 68-82 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office Action contended that the specification lacks sufficient guidance on how to make the claimed compounds wherein the variables are heteroaryl.

While Applicants respectfully disagree with this rejection, in order to expedite prosecution, instant claim 1 herein does not recite that R_5 can be heteroaryl or that R_{10} can be heteroaryl. Consequently, Applicants assert that the instant claim 1, and the claims that depend therefrom, are herein enabled by the specification.

Accordingly, Applicants request reconsideration and withdrawal of the rejection under § 112.

III. THE REJECTIONS UNDER 35 U.S.C. § 103 ARE OVERCOME

Claims 1, 68, and 72 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Hamel et al. (Curr Med Chem – Anti-Cancer Agents 2002, 2) and Wolff et al. (Burger's Medicinal Chemistry and Drug Discovery, 5th Ed., vol. 1, 1995, 974-977). Claims 1, 68, and 72 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Sasse et al. (J Antibiotics 2000, 53: 879-885) and Wolff et al. Claims 1, 68, and 72 were also rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Hoefle et al. (DE 10008089) and Wolff et al. Further, claims 1, 68, and 72 were also rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Hoefle et al. (DE 19638870) and Wolff et al. These rejections are traversed and will be addressed collectively.

Applicants respectfully remind that the Supreme Court has recently reaffirmed the factors set out in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18: "[T]he scope and content of the prior art are determined; differences between the prior art and the claims at issue are…ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727. Furthermore, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Office Action does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Applying the law to the instant facts, the references relied upon by the Office Action do not render the presently claimed invention obvious. The Office Action alleged that the claimed compounds are prodrugs of the compounds of the cited references, and a skilled artisan would therefore be motivated to prepare the claimed compounds. Applicants respectfully disagree.

Applicants note that a prodrug is typically defined as a pharmacological substance that is administered in an inactive, or significantly less active, form (*see, e.g.*,

http://en.wikipedia.org/wiki/Prodrug; enclosed herein as Exhibit A). While a prodrug can be converted into its active form in the body by normal metabolic processes, the prodrug is the inactive precursor. With this in mind, Applicants assert that there would be no motivation to modify the compounds of the cited references to arrive at the claimed compounds, nor is the modification simple, as the claimed compounds are not prodrugs.

Applicants refer to the Declaration under 37 C.F.R. § 1.132 by Wolfgang Richter that accompanied the Amendment and Response to Office Action filed on May 22, 2009. According to the Declaration, compounds wherein group R is a group of formula OR_1 and wherein R_1 is not a hydrogen atom are significantly more active than the responding compounds wherein R is an OH- group. For instance, in the Declaration, Derivatives 2 and 3, wherein group R is a group of formula OCH_2CH_3 or OCH_3, show IC_{50} values of 0.02 while natural Tubulysin A shows an IC_{50} of 0.2. Accordingly, the ester derivatives of Tubulysin A have a ten-fold higher activity. Derivative 6 carrying an $OCH_3CH_2CH_3$ group shows an IC_{50} value of 0.05, *i.e.*, is four times as active as Tubulysin A. In addition, Derivative 5, which is the ethyl ester derivative of Derivative 4, has an IC_{50} value of 0.04 whereas the acid Derivative 4 shows an IC_{50} value of 0.01.

As demonstrated by the Declaration, ester derivatives of the Tubulysins that are encompassed by the invention accordingly to claim 1 have a significantly increased activity when compared with the acid derivatives. Therefore, the compounds of the instant claims cannot be considered to be prodrugs of the compound of the cited references. The Office Action thereby does not provide any motivation for arriving at the claimed invention from the cited references. There is no disclosure of the claimed compounds in the cited references, individually or combined, and the elevated activity of the claimed compounds could not be predicted based on the cited references.

Accordingly, Applicants assert that the claimed invention is not obvious in view of the cited references. Applicants thereby request reconsideration and withdrawal of the Section 103 rejections.

CONCLUSION

Applicants believe that the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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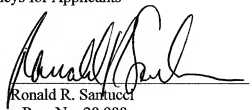
By: 

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